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# Effect of voriconazole on the pharmacokinetics and pharmacodynamics of zolpidem in healthy subjects

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**Aims**
To assess the effect of voriconazole on the pharmacokinetics and pharmacodynamics of zolpidem.

**Methods**
In a randomized cross-over study with two phases, 10 healthy subjects ingested 10 mg of zolpidem with or without oral voriconazole pretreatment. The concentrations of zolpidem were measured in plasma up to 24 h and pharmacodynamic variables were monitored for 12 h.

**Results**
Voriconazole increased the peak plasma concentration of zolpidem by 1.23-fold [$P < 0.05$; 90% confidence interval (CI) 1.05, 1.45] and the area under the plasma zolpidem concentration–time curve by 1.48-fold ($P < 0.001$; 90% CI 1.29, 1.74). The time to peak plasma zolpidem concentration was unchanged by voriconazole but the half-life was prolonged from 3.2 to 4.1 h ($P < 0.01$; 95% CI on the difference 0.27, 1.45). The pharmacodynamics of zolpidem were unaffected by voriconazole.

**Conclusion**
Voriconazole caused a moderate increase in exposure to zolpidem in healthy young subjects but no clear pharmacodynamic changes were observed between the groups.

## Introduction

Zolpidem is widely used for the treatment of insomnia. It is rapidly absorbed from the gastrointestinal tract and has an oral bioavailability of approximately 70% [1]. Zolpidem is extensively metabolized in humans by cytochrome P450 (CYP) 3A4, CYP2C9 and CYP1A2 [2] and it has an elimination half-life of 2.0–2.2 h [3]. Elimination is impaired in the elderly and in patients with liver or kidney disease [1]. Voriconazole is a relatively new agent used to treat invasive fungal infections both intravenously and orally [4]. Voriconazole is rapidly and almost completely absorbed from the gastrointestinal tract [5] and undergoes extensive oxidative metabolism involving CYP2C9, CYP2C19 and CYP3A4 [6]. The drug inhibits several CYP enzymes [7, 8] and we have previously shown that it interacts strongly with the CYP3A4 substrate, midazolam [9]. The extensive CYP-mediated metabolism of zolpidem has implications for its susceptibility to metabolic drug interactions. Because voriconazole inhibits several of the CYP enzymes that are involved in the metabolism of zolpidem, the possible effects of voriconazole on the pharmacokinetics and pharmacodynamics of oral zolpidem were investigated.

## Methods

### *Study design*

The study protocol was approved by the Ethics Committee of our Hospital District and by the National Agency of Medicines, Finland. Written informed consent was obtained from 10 healthy males (age range 19–29 years; weight range 67–100 kg) prior to entry into the study. They were ascertained to be in good health by medical history, clinical examination and routine laboratory tests. None of the subjects was receiving any continuous medication or was a smoker.

An open, randomized, two-phase, cross-over study design at an interval of 1 week was used. All subjects ingested 10 mg of oral zolpidem (Stilnoct; Sanofi-Synthelabo, Bromma, Sweden) with or without oral voriconazole (Vfend; Pfizer, Sandwich, UK) pretreatment. The dose of voriconazole was 400 mg twice daily for 1 day and then 200 mg twice daily for a second day. Zolpidem was administered at 09.00 h, 1 h after the last dose of voriconazole. The subjects fasted for 12 h before the administration of zolpidem and were given standard meals 4 h and 8 h later. Subjects were asked not to drink grapefruit juice, alcohol, coffee, tea or cola for 2 days prior to the study and on the test days.

### *Sampling and drug analysis*

Blood samples were drawn from a cannulated forearm vein into ethylenediaminetetraacetic acid tubes immediately before the last voriconazole dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h after zolpidem administration. Plasma was separated within 30 min and stored at −40 °C until analysis.

After preparation of plasma samples [10], chromatography was performed using a C8 column and a mobile phase consisting of ammonium formate (pH 4.0), acetonitrile (20%) and water (80%). Zolpidem was detected using tandem mass spectrometry. The limit of quantification was 0.25 ng ml$^{-1}$ and the interday coefficient of variation (CV) was 8.3–13.7% ($n = 12$). Voriconazole was determined by high-performance liquid chromatography [11, 12] and the limit of quantification was 20 ng ml$^{-1}$ and the CV 0.7–3.7% ($n = 3$).

### *Pharmacokinetic analysis*

The peak plasma concentrations ($C_{max}$) and times to $C_{max}$ ($t_{max}$) were obtained directly from the data. The areas under the zolpidem plasma concentration–time curves $AUC_{0-\infty}$ were estimated using the trapezoidal rule with extrapolation to infinity. For each subject, the terminal log-linear phase of the plasma zolpidem concentration–time curve was identified visually and the elimination rate constant ($k_e$) was determined by regression analysis. The elimination half-life ($t_{1/2}$) was calculated from the equation: $t_{1/2} = \ln 2/k_e$.

### *Pharmacodynamic measurements*

Subjective effects were recorded using three visual analogue scales and the Maddox wing test at the time of blood sampling and up to 12 h after zolpidem administration as described earlier [9]. For each pharmacodynamic variable, the area under the response–time curve was determined by the trapezoidal rule for 12 h.

### *Statistical analysis*

Student's paired *t*-test was used and differences were regarded as significant if $P < 0.05$. Geometric mean ratios with 90% confidence intervals (CIs) and 95% CIs on the differences between the control and voriconazole phases were calculated. The results are expressed as mean values ± SD, except in Figure 1, where, for clarity, mean values ± SEM are given.

## Results

The $C_{max}$ and $AUC_{0-\infty}$ (in all subjects) of oral zolpidem were increased (geometric mean ratio) 1.23-fold ($P < 0.05$; 90% CI 1.05, 1.45) and 1.48-fold ($P < 0.001$; 90% CI 1.29, 1.74), respectively, by voriconazole (Figure 1a, Table 1). The $t_{1/2}$ of zolpidem was prolonged from 3.2 to 4.1 h ($P < 0.01$; 95% CI on the difference 0.27, 1.45), but $t_{max}$ did not change after voriconazole pretreatment. The mean value of $C_{trough}$ of voriconazole was 596 ng ml$^{-1}$ (range 249–1517) during pretreatment with this drug. Although voriconazole appeared to increase drowsiness in the immediate period following the administration of zolpidem, no statistically significant differences between the phases were seen in any of the pharmacodynamic variables (Figure 1b). All volunteers completed the study, but transient visual adverse events were reported by each of the 10 subjects and transient headache was reported by one after starting voriconazole.

## Discussion

Coadministration of voriconazole moderately affected the pharmacokinetics of oral zolpidem by increasing its $C_{max}$ by 1.2-fold and $AUC_{0-\infty}$ by 1.5-fold. Although voriconazole appeared to increase the sedative effects of zolpidem transiently, no statistically significant differences were seen in any of the pharmacodynamic variables.

Earlier studies with antifungals have shown that their effects on zolpidem pharmacokinetics are clearly weaker than those on midazolam or triazolam [13–15]. Ketoconazole and itraconazole increase the mean $AUC_{0-\infty}$ of

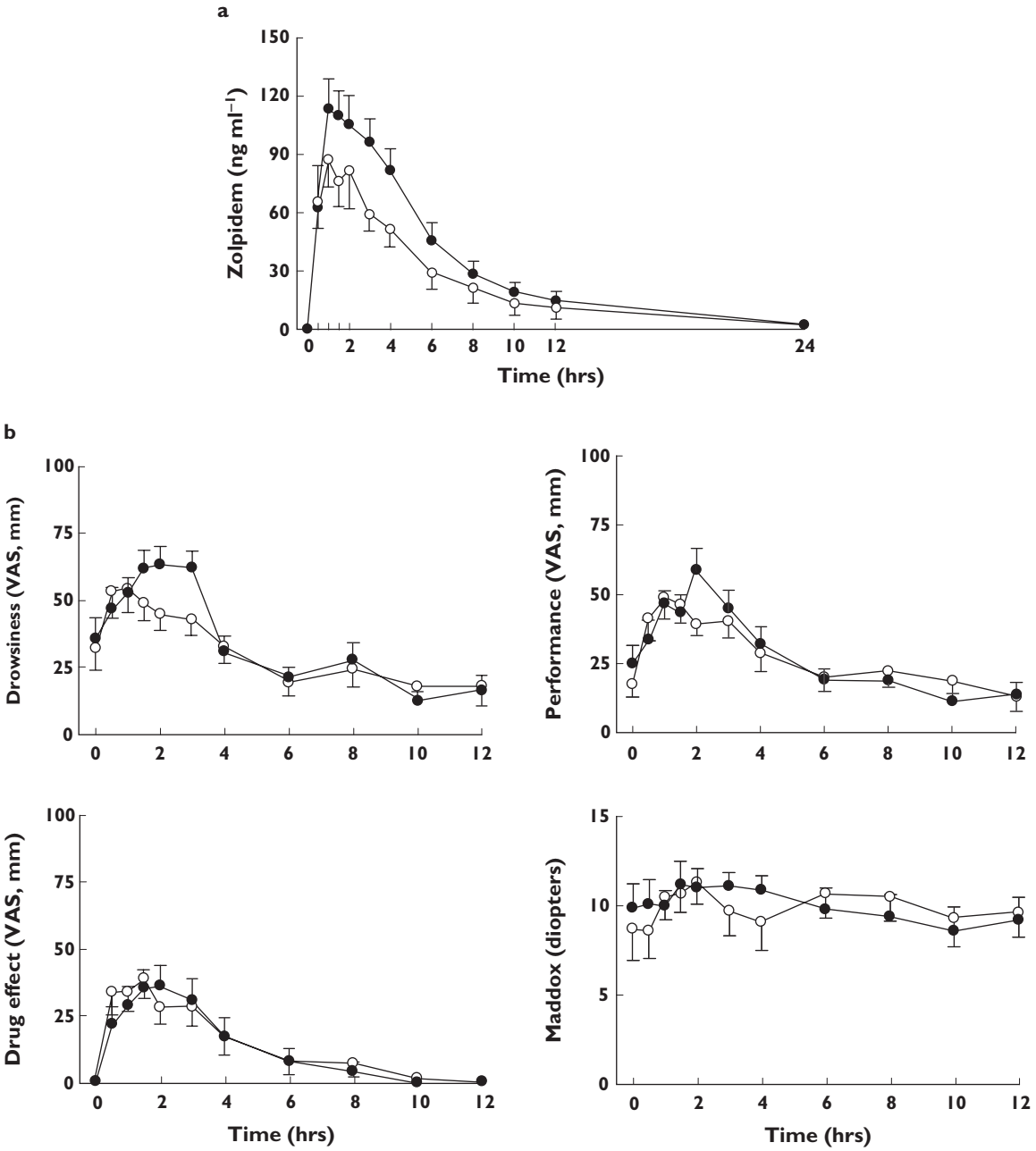


**Figure 1**

(a) Plasma concentrations (mean ± SEM) of zolpidem after an oral dose of 10 mg of zolpidem without (○) or following pretreatment with oral voriconazole (400 mg twice daily on the first day and 200 mg twice daily on the second day; ●) to 10 healthy males, and (b), the results of drowsiness, performance and subjective drug effect data obtained from visual analogue scales (VAS) and the Maddox wing test

zolpidem by 1.7- and 1.3-fold, respectively [13]. In the present study with voriconazole, we observed a 1.5-fold increase in the zolpidem $AUC_{0-\infty}$. Ketoconazole, itraconazole and voriconazole cause at least a 10-fold increase in the mean $AUC_{0-\infty}$ of oral midazolam and also statistically enhance its sedative effects [9, 14]. Correspondingly, itraconazole increases the $AUC_{0-\infty}$ of oral triazolam by 27-fold [15]. Similar differences have been observed after ritonavir administration, which increases the $AUC_{0-\infty}$ of oral triazolam 27-fold but that of zolpidem only 1.3-fold [16]. Because oral midazolam and triazolam are significantly metabolized during first-pass, the inhibition of this process causes a considerable increase in the midazolam and triazolam concentrations. The oral

**Table 1**
Pharmacokinetic parameters for zolpidem (10 mg administered orally) without (control) and following pretreatment with oral voriconazole (400 mg twice daily on the first day and 200 mg twice daily on the second day) to 10 healthy males

| Parameter | Control phase | Voriconazole phase | 95% CI on the difference between phases | Geometric mean ratio and 90% CI |
|---|---|---|---|---|
| *Zolpidem* | | | | |
| $C_{max}$ (ng ml$^{-1}$) | 112 ± 50 | 135 ± 47* | 0.32, 45.3 | 1.23 (1.05, 1.45) |
| % of control (range) | 100 | 120 (90–147) | | |
| $t_{max}$ (h) | 1 (0.5–4.0) | 1.5 (0.5–3.0) | | |
| $AUC_{0-\infty}$ (ng ml$^{-1}$ h) | 528 ± 337 | 743 ± 412† | 119, 310 | 1.48 (1.29, 1.74) |
| % of control (range) | 100 | 141 (117–288) | | |
| $t_{1/2}$ (h) | 3.2 ± 1.8 | 4.1 ± 1.6‡ | 0.27, 1.45 | 1.35 (1.15, 1.62) |
| % of control (range) | 100 | 128 (100–270) | | |

*Data are presented as mean±SD, except for $t_{max}$, presented as median and range. CI, Confidence interval; $C_{max}$, peak plasma concentration; $t_{max}$, time to peak plasma concentration; $AUC_{0-\infty}$, area under the zolpidem plasma concentration–time curve; $t_{1/2}$, elimination half-life. *Significantly ($P < 0.05$) different from control. †Significantly ($P < 0.001$) different from control. ‡Significantly ($P < 0.01$) different from control.*

bioavailability of zolpidem (70–80%) is higher than that of midazolam (30%) or triazolam (30–40%) [9, 17]. Unlike midazolam and triazolam, zolpidem is only partially metabolized by CYP3A [3]. Accordingly, inhibition of the CYP3A-mediated metabolism of zolpidem may be compensated to some degree by an unaffected pathway.

Despite statistically significant changes in the pharmacokinetics of zolpidem induced by voriconazole, the increased concentrations of the former drug were not associated with increased psychomotor effects. This can be rationalized because of the log-linear relationship of the concentration *vs.* response curves. Thus, small differences in drug concentrations will not result in changes of drug effects. Because a double-blind study design was not used, the pharmacodynamic findings must be interpreted cautiously. However, since the subjects were well-informed medical students, even a double-blind study design may not have increased the validity of the pharmacodynamic results.

Our study was performed in young healthy males and therefore the results cannot be extrapolated with confidence to elderly patients or patients with critical illness. It was shown recently that the clearance of zolpidem is substantially diminished in the elderly, particularly in men [18]. Voriconazole is currently used in critically ill patients with extensive fungal infections, and these patients can be very sensitive to the CNS depressant effects of drugs such as zolpidem. Thus, the increase in plasma zolpidem concentrations after voriconazole administration may have serious effects in critically ill patients.

In conclusion, voriconazole caused modest increases in the plasma concentrations and elimination half-life of orally administered zolpidem. Further studies are needed to investigate whether our results can be extrapolated to elderly patients and patients having severe systemic diseases.

*Competing interests: None declared.*

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